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1 **Understanding the effects of air pollution on neurogenesis and gliogenesis in the**
2 **growing and adult brain**

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16

17 **Abstract**

18 Exposure to air pollution – and particularly to particulate matter (PM) – is strongly
19 associated with higher risk of neurodevelopmental disorders, poor mental health and
20 cognitive defects. In animal models, disruption of CNS development and disturbances of
21 adult neurogenesis contribute to PM neurotoxicity. Recent studies show that gestational
22 PM exposure not only affects embryonic neurodevelopment, but also disturbs postnatal
23 brain growth and maturation, by interfering with neurogenic/gliogenic events, myelination
24 and synaptogenesis. Similarly, adult neurogenesis is affected at many levels, from neural
25 stem cell amplification up to the maturation and integration of novel neurons in the adult
26 brain parenchyma. The underlying mechanisms are still by and large unknown. Beyond
27 microglia activation and neuroinflammation, recent studies propose a role for novel
28 epigenetic mechanisms, including DNA methylation and extracellular vesicles-associated
29 microRNAs.

30 Exposure to air pollution is increasingly acknowledged as one of the main contributors to
31 the global disease burden [1]. It has been estimated that in 2016 91% of the world
32 population was living in places where the WHO air quality guidelines levels were not met
33 ([https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)
34 [health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)). Among the key air pollutants that pose health risks, particulate matter (PM) is one
35 of the most widespread. PM is a heterogeneous mixture of small solid or liquid particles
36 released into the atmosphere during combustion processes or emitted by industrial
37 activities and natural sources. PM generally comprises water soluble and insoluble
38 components, including inorganic compounds, polycyclic aromatic hydrocarbons, heavy
39 metals and other toxic substances, and microbial components, such as bacteria and their
40 products of degradation (e.g. lipopolysaccharide) and viruses [2]. PM is defined according
41 to its aerodynamic diameter, with coarse PM smaller than 10 μm (PM_{10}) and fine and
42 ultrafine PM smaller than 2.5 ($\text{PM}_{2.5}$) or 0.1 ($\text{PM}_{0.1}$) μm , respectively. Thanks to their small
43 size, when inhaled, PM particles have the capability to percolate through the respiratory
44 tract. While PM_{10} is trapped in the upper airways, $\text{PM}_{2.5}$ reaches the lungs and deposits in
45 the alveolar area. Ultrafine particles could even penetrate into the blood circulation and
46 overcome the blood-brain-barrier (BBB) [3,4], or pass through the nasal mucosa and
47 directly enter the brain [5,6]. Of note, inhaled nanoparticles have been shown to cross the
48 placental barrier and to deposit in the fetal tissues in animal models [7], suggesting a
49 possible mother-to-fetus transfer of airborne ultrafine PM.

50 Chronic exposure to air pollution has been consistently associated with risk of
51 cardiovascular and respiratory diseases, and different types of cancer [1]. Increasing
52 evidence also indicates that the central nervous system (CNS) is a target for air pollution.
53 In utero and early child exposure to high levels of air pollution, and in particular to PM, is
54 associated with higher risk of neurodevelopmental disorders, long-lasting behavioral
55 alterations and cognitive defects [8,9]. Moreover, during adulthood, chronic PM exposure

56 has been associated with poor mental health, increased risk of onset and worsening of
57 depression [9], while both short and long term exposure has been associated with
58 cognitive/memory deterioration [10,11].

59 Most studies in animal models that aimed at establishing a causative link between air
60 pollution and anatomical/functional CNS alterations, and at unveiling the underlying
61 mechanisms, are focused on the effects of PM. In rodents, PM exposure results in
62 neurodevelopmental, cognitive and behavioral alterations reminiscent of those observed in
63 humans, whose extent and duration depend on PM size, doses and timing of exposure
64 [12–17]. Mechanistically, disruption of CNS development and of adult neurogenesis were
65 found to contribute to PM detrimental effects, suggesting the occurrence of similar events
66 in humans.

67 In this review, we summarize recent advancements toward the understanding of the
68 cellular and molecular mechanisms mediating PM effects on the developmental and adult
69 neurogenesis and gliogenesis, discuss limitations of the available studies and highlight
70 persisting open issues.

71

72 **In utero and neonatal exposure to PM induces neurodevelopmental alterations in** 73 **animal models**

74 In mice, chronic prenatal exposure to high levels of fine and ultrafine PM was reportedly
75 associated with reduced brain weight and ventriculomegaly at birth and during the first
76 postnatal period [13,18]. This is the outcome of the disruption of specific and diverse
77 neurodevelopmental events. Exposure to diesel exhaust particles (DEP) in mouse
78 pregnant dams throughout gestation resulted, in the offspring, in increased cortical (i.e.
79 prefrontal cortex) and hippocampal (i.e. dentate gyrus, DG) volumes at embryonic day
80 (E)18, which switched to decreased cortical volume and normalized hippocampal size in
81 postnatal day (P)30 males (but not in females), compared to untreated animals [19].

82 Similarly, maternal inhalation of carbon black nanoparticles (produced by the incomplete
83 combustion of petroleum products) resulted in an initial increase of parvalbumin-positive
84 (+) neurons in the uppermost layers of the motor cortex, followed by a large reduction at
85 later time points [20]. These results suggest that gestational PM exposure may
86 differentially affect distinct phases of brain development and cause an initial tissue
87 overgrowth – possibly due to neural stem cell (NSC)/progenitor over-expansion - followed
88 by postnatal regressive events. Thus, the effects on CNS development of in utero PM
89 exposure can be persistent and extend beyond the embryonic period. In line with this
90 interpretation, two recent studies [12,21] have shown that chronic prenatal exposure to
91 high dosages of PM_{2.5} resulted in increased neuronal and astrocyte apoptosis in the cortex
92 and distinct hippocampal subregions, including the DG, of the offspring at P14-P30.
93 Postnatal hippocampal neurogenesis and astrogliogenesis appeared also dramatically
94 reduced, due to the suppression of NSC proliferation in the subgranular zone (SGZ).
95 Similarly, parenchymal astro- and oligo-dendroglia amplification was affected, as indirectly
96 assessed by the large decrease of the proliferation marker PCNA in the cortex of P1-P30
97 offspring [21]. In agreement with this finding, gestational chronic exposure to fine and
98 ultrafine particles has been associated with precocious myelination and premature
99 oligodendroglia proliferation/differentiation switch in the corpus callosum of the adolescent
100 offspring [13,22]. Dendritic complexity [15] and number of asymmetric excitatory synapses
101 impinging on hippocampal neurons were also significantly reduced in adolescent (P14)
102 mice prenatally exposed to PM_{2.5}. The remaining synapses showed altered -and possibly
103 compensatory- features, including increased number of presynaptic vesicles, thickened
104 postsynaptic density and decreased synaptic space [12].

105 Thus, gestational PM exposure not only affects embryonic neurodevelopment, but also
106 disturbs postnatal brain growth and maturation, by interfering with neurogenic/gliogenic
107 events, myelination and synaptogenesis. Pregnancy appears to be a particularly

108 vulnerable time window, since neonatal exposure had milder effects, and mostly affected
109 myelination [23,24] and expression of synaptic proteins [14].

110 111 **PM exposure disturbs adult neurogenesis in animal models**

112 In the adult mouse brain, generation of new neurons continues in the subventricular zone
113 (SVZ) of the lateral ventricles and in the SGZ of the hippocampus [25]. Adult neurogenesis
114 in the SVZ cannot be detected in humans, whereas controversial evidence has been
115 provided about the generation of new neurons in the adult human hippocampus [26–28].
116 Thus, while adult hippocampal neurogenesis is implicated in cognitive processes and
117 mood regulation in rodents [29], whether this occurs also in adult humans is highly
118 debated. Nevertheless, adult neurogenesis in rodents recapitulates many aspects of the
119 developmental neurogenic/gliogenic events. Therefore, the study of the mechanisms
120 mediating PM-induced perturbations of the adult neurogenic niches is still of interest, as it
121 can unveil critical toxicity processes operating in both developing and mature CNS.

122 In a recent study, acute exposure to fine DEP caused an impairment of adult neurogenesis
123 in mice. This effect was gender-specific, with males showing fewer newly-generated
124 neurons in SGZ, SVZ and olfactory bulb (OB), compared to control animals, and females
125 displaying fewer new neurons only in the OB [30]. Reduced neurogenesis was a
126 consequence of decreased proliferation of NSCs/progenitors, reduced survival of
127 immature neurons, and altered specification/differentiation of newborn elements (i.e.
128 reduced fraction of newborn cells expressing the mature neuronal marker NeuN 3 weeks
129 after their generation [30]). Moreover, life-long exposure to concentrated water-soluble
130 subfraction of PM_{0.2} dramatically reduced the number of SGZ newborn neurons -but not of
131 newborn astrocytes- in adult male rats, which also showed contextual memory defects and
132 depressive behaviors [16]. Thus, PM appears to negatively modulate the neurogenic
133 events at many levels, from NSCs division up to the maturation and integration of novel

134 neurons in the adult brain parenchyma. In line with this view, chronic inhalation of
135 ammonium sulfate, the major inorganic component in PM_{2.5} (as resulting from the reaction
136 of ammonia, mostly originating from animal farming and synthetic fertilizers, with sulfur
137 dioxide emitted by the burning of fossil fuels [31]), diminished the dendritic complexity of
138 immature neurons in the DG of aged rats [32]. However, in this latter study, no alteration of
139 SGZ/SVZ NSC/progenitor proliferation and of the specification of their derivatives could be
140 detected, highlighting a specific neurotoxicity of the distinct components of PM.

141

142 **Proposed mechanisms underlying the effects of PM on neurogenesis and** 143 **gliogenesis**

144 In rodents, neuroinflammation accompanied by microglia and astrocyte activation were
145 cardinal effects of PM exposure, whenever it occurs [12–16,19,20,23,24,30].
146 Pharmacological treatments aimed at blocking microglia polarization – such as the
147 peroxisome proliferator-activated receptor γ (PPAR γ) agonist pioglitazone - protected
148 against PM-induced suppression of SGZ proliferation and rescued the number of newborn
149 neurons, indicating a major role of microglia reactivity in the negative modulation of adult
150 hippocampal neurogenesis [30]. Nevertheless, mechanistically, which activated microglia
151 phenotype (i.e. proregenerative M2 vs. neurotoxic M1 vs. “dark microglia” [33]) is favored
152 upon/after PM exposure and how microglia activation inhibits the neurogenic events
153 remain obscure. Beyond the release of high levels of pro-inflammatory cytokines or
154 reactive oxygen species, that can inhibit NSC/progenitor proliferation and alter the
155 specification and survival of their derivatives [34], an interesting hypothesis is that PM-
156 induced microglia activation could result in increased phagoptosis (i.e. the engulfment of
157 immature viable neurons [35]). In line with this hypothesis, Bolton and colleagues [19]
158 reported increased microglia-neuron physical interactions in the cortex of the offspring of
159 PM-exposed dams.

160 Notably, upon prenatal and neonatal PM exposure, microglia activation and astrogliosis
161 occurred predominantly in males [19,23,24,36]. Consistently, neuroinflammation was more
162 pronounced in males than in females upon exposure to DEP during adulthood [37], in line
163 with a more marked reduction of adult neurogenesis [30]. This suggests that sex-
164 dependent factors, including the hormonal background, may influence the individual's
165 vulnerability to PM effects. Interestingly, microglia activation and neuroinflammation
166 extended well beyond PM-exposure, when it occurred in utero, in line with a priming action
167 of air pollution.

168 Moreover, what is the trigger for microglia and astrocyte activation remains elusive. Fine
169 and ultrafine particles could enter the CNS and directly stimulate glial reactivity. Given the
170 relatively small extension of the olfactory mucosa, it is likely that in humans – at difference
171 with rodents - the main entrance route for PM is the blood. In line with this view, astroglia
172 reactivity was observed predominantly around blood vessels [38]. Nevertheless, glial cells
173 and NSCs/progenitors may be reached by a plethora of other factors – and even cells-
174 from the periphery, thanks to the disruption of BBB integrity and increased leakage
175 induced by PM exposure [13,16]. Among these elements, pulmonary cell-derived
176 extracellular vesicles (EVs) may represent important lung-to-brain mediators of PM effects
177 [39,40]. EVs are lipid bilayer-delimited particles, actively released from cells in response to
178 stress. After internalization within target cells, EVs deliver their content, including proteins,
179 lipids and miRNAs, and profoundly influence the recipient cell molecular state and function
180 [41]. Interestingly, recent studies [39,40] showed that, in humans, the miRNA cargo of
181 plasma EVs released following PM exposure has a signature relevant for the modulation of
182 glial cell reactivity (e.g. miR-9, involved in microglia activation and neuroinflammation [42])
183 and NSC/progenitor functions (e.g. miR-128, miR-302, let-7 and miR-9, regulating neural
184 precursor proliferation and neurogenesis [43]; miR-21, miR-9, miR-200, miR-17, miR-7,
185 miR-302c, limiting oligodendroglia differentiation or enriched in immature oligodendrocyte

186 precursors [44]). Finally, a novel epigenetic mechanism possibly mediating PM effects on
187 developmental and adult neurogenesis may be the regulation of DNA methylation in NSCs
188 and their derivatives, that has been shown to be responsive to extrinsic signals and to
189 influence multiple aspects of neurogenesis from stem cell maintenance up to
190 synaptogenesis [45]. This hypothesis is corroborated by the observation of increased DNA
191 methyltransferase DNMT1 in the brains of male mice perinatally exposed to DEP [46].
192 Notably, in human placenta, PM exposure was associated with altered methylation level of
193 DNA repair and clock genes [47,48], which are also essential for adult and developmental
194 neurogenesis [49–51].

195

196 **Concluding remarks and open issues**

197 Convincing evidence, obtained in animal models, shows that CNS development and adult
198 neurogenesis are profoundly impacted by PM exposure throughout life, with significant
199 behavioral and cognitive alterations. This field of research is still in its infancy and
200 strenuous efforts are still needed to clarify the precise mechanisms by which PM affects
201 neurodevelopmental events and adult neurogenesis, and the molecular substrates of
202 gender and time window -specific differences in PM sensitivity. Available mechanistic
203 studies have frequently exploited heterogeneous PM dosages, composition, administration
204 modalities and timing. This scenario has so far impeded a complete understanding of the
205 processes subserving PM effects. Nevertheless, research on the effects of PM on other
206 systems has greatly advanced in the last years and identified interesting candidate
207 mechanisms that could be also at the basis of PM neurotoxicity.

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410 *polymorphisms of reelin are associated with Autism Spectrum Disorder (ASD) and*
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445

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447 The authors declare no conflict of interest. The funding sponsors had no role in the
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449 **Figure legend**

450 **Figure 1. PM-induced alterations detected in the adult mouse brain following in-**
451 **utero or adult exposure.** Orange boxes (above) include the proposed underlying
452 mechanisms. BBB, blood-brain barrier; CC, corpus callosum; DG/SGZ, hippocampal
453 dentate gyrus/subgranular zone; EV, extracellular vesicles; NSCs, neural stem cells; OPC,
454 oligodendrocyte precursor cell; PM, particulate matter; PV, parvalbumin.

Microglia
& astrocyte
reactivity

BBB
breakdown

EV-associated
miRNAs

DNA methylation

In-utero PM exposure



Effects in young adults

CORTEX

- volume
- PV+ neurons
- proliferation



↑ apoptosis
of neurons
and astrocytes

CC



↓ OPC
expansion



↑ OPC
maturation &
myelination

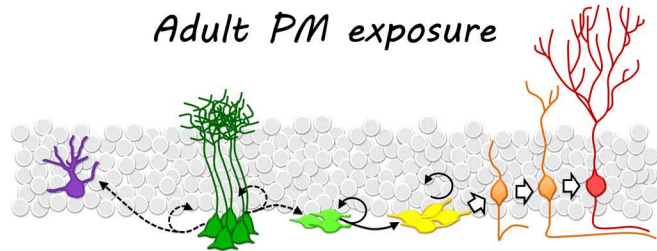
DG/SGZ

- proliferation
- dendritic
complexity



↑ apoptosis
of neurons
and astrocytes

Adult PM exposure



NSCs/intermediate
progenitors:

↓ proliferation

Unaltered
astroglialogenesis

Newborn neurons:

-survival

-acquisition of
mature markers

-dendritic
complexity

